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EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,793	JOHANSEN ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-83 and 87-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-83 and 87-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 9/9/08 is acknowledged. Claims 1-79 and 84-86 are cancelled. Claims 80 and 91-93 are amended. Claims 80-83 and 87-93 are pending in this application and under examination in this office action.

2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

3. Applicant's arguments filed on 9/9/08 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

4. The rejection of claims 80-83 and 87-93 under 35 U.S.C. 112, second paragraph, for being indefinite is withdrawn in response to Applicant's amendment to the claims.

Claim Rejections/Objections Maintained

In view of the amendment filed on 9/9/08, the following rejections are maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 80-83, 87-90 and 93 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,749 (Yan) in view of US 6,284,540 (Milbrandt et al). The rejection is maintained for the reasons made of record.

On p. 5-8 of the response, Applicant argues that neublastin/artemin (NBN/ARTN) is structurally and functionally distinct from GDNF because NBN/ARTN only binds to GFRα3 with high affinity, and GDNF only binds to GFRα1 but does not bind to GFRα3. Applicant further cites WO2000/01815, Rakowiez (J. Neurosci. 2002. 22: 3953-62), and Carmillo (Biochemistry. 2005. 44: 2545-54) in support of the arguments. Applicant arguments have been fully considered but they are not persuasive.

In contrast, although NBN/ARTN binds to GFRα3, Milbrandt (US 6,284,540) also teaches that NBN/ARTN can bind and activate GFRα1 (figure 11; examples 7-8). The binding of NBN/ARTN to GFRα1 is also supported by Carmillo (see abstract) regardless of whether Carmillo was able to reproduce the data of activation of GFRα1 by ARTN. Thus, not only does NBN/ARTN belong to the GDNF family, it also functions as GDNF.

In this case, the combined teachings of Yan and Milbrandt do render the instant method obvious. Yan (US 5,641,749) teaches a method of treating retinal ganglion cell

degeneration caused by glaucoma by the intraocular implantation of glial cell line-derived neurotrophic factor (GDNF)-expressing cells (see paragraph spanning columns 4-5, and column 19, lines 28-30) and Milbrandt teaches that NBN/ARTN is a member of the GDNF family, which functions similarly to other members of the family, and has been shown to be able to bind and activate GFRα1 (i.e. the receptor for GDNF). Thus, it would have been obvious to use NBN/ARTN or cells expressing NBN/ARTN as disclosed by Milbrandt to replace GDNF in the Yan's method because substitution of GDNF with NBN/ARTN is expected work in treatment of glaucoma or retinal degeneration. Note that it is obvious to combine prior art elements according to known methods to yield predictable results and it is also obvious as to simply substitute one known element for another to obtain predictable results.

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.,* 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

On p.8 of the response, Applicant argues that there is no motivation or suggestion to combine the applied references to achieve the claimed method because Milbrandt does not teach a method of treating Neublastin/artemin in treatment of macular degeneration, glaucoma or retinitis pigmentosa and Yan only teaches use of GDNF in treatment of retinal ganglion cell degeneration. Applicant also cites *DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Col, SIBA Neuroscience, Inc.*

v. Cadus Pharma. Corp., In re Fulton and *KSR* in support of the arguments. Applicant arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument with regard to no motivation to combine, it is noted that "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdiqital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

In addition, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP. §2144.07.

In this case, Yan discloses methods of treating retinal ganglion cell degeneration caused by glaucoma by the intraocular implantation of glial cell line-derived neurotrophic factor (GDNF)-expressing cells (see paragraph spanning col. 4-5, and column 19, lines 28-30). Although Yan does not teach use of NBN/ARTN, Milbrandt teaches that NBN/ARTN is a member of the GDNF neurotrophic factor family and is useful for treating conditions involving neuronal degeneration including degeneration of

retina (i.e. a type of neuron). Since NBN/ARTN is a member of the GDNF family and can bind and activate GFRα1 (i.e. the receptor for GDNF), it would have been expected that NBN/ARTN would act and function as GDNF and would be effective in treatment of retinal degeneration as GDNF as disclosed by Yan. Accordingly, the rejection is maintained.

8. Claims 80-83 and 87-93 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,749 (Yan) in view of US 6,284,540 (Milbrandt) as applied to claims 80-83, 87-90 and 93 above, and further in view of US 6299895 (Hammang). The rejection is maintained for the reasons made of record.

On p. 9 of the response, Applicant argues that the combined references would not achieve the claimed invention because Yan discloses treatment of eyes disorders using, which is a structurally different protein from the claimed protein, Milbrandt does not teach the treatment of an eye disorder by NBN/ARTN, and Hammang does not NBN/ARTN in the treatment of macular degeneration or retinitis pigmentosa. Applicant's arguments have been fully considered but they are not persuasive.

In response, as set forth above, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

In contrast, as previously made of record and as set forth above, Yan teaches a method of treating retinal ganglion cell degeneration caused by glaucoma with GDNF. In addition, Hammang (US6299895) teaches use of GDNF in treatment of macular

degeneration and retinitis pigmentosa as recited in instant claims 80, 91 and 92 (see col.5, lines38-64; col. 10, line 16-col.11, line 67; examples 1-5). Although Yan and Hammang do not teach use of NBN/ARTN, Milbrandtl teaches that NBN/ARTN is a member of the GDNF family and can bind and activate GFRα1. Thus, substitution of GDNF with NBN/ARTN in the methods of Yan and Hammang would have been expected to work as GDNF because NBN/ARTN is a member of the GDNF family and can act as GDNF by binding and activating GFRα1.

New Grounds of Rejection Necessitated by the Amendment

The following rejections are new grounds of rejections necessitated by the amendment filed on 3/27/08.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-83 and 87-93 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating photoreceptor loss in the retina of patients afflicted with macular degeneration, retinitis pigmentosa, or glaucoma, comprising administering to the eye of said patient a cell line expressing a Neublastin polypeptide comprises one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 9-12, does not reasonably provide enablement for a method of treating the above eye disorders comprising administering a cell line

expressing a Neublastin polypeptide, which comprises an amino acid sequence that is at least 95% homologous to the amino acid sequence of SEQ ID NO: 12 or comprising any amino acid sequences of SEQ ID NOs 9-12 (i.e. including undefined fragments) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is reinstated and maintained for the reasons below.

On p. 10-14 of the response, Applicant argues that the examiner does not provide evidence that the claimed NBN polypeptides would not have neurotrophic activity and thus to be used in the claimed method. Applicant also argues that the instant specification provides multiple assays for a skilled artisan to determine whether an amino acid sequence at least 95% identical to SEQ ID NO:12 would have the desired activity. Applicant also argues that the cited reference of Burgess is irrelevant because it does not teach a method of treating an eye disorder using a cell line expressing NBN. Applicant further cites *In re Wright, In re Marzocchi, In re Morehouse, In re Chilowsky and PPG Indus., Inc. v. Guardian Indus. Corp.* in support of the arguments.

In response, to determine whether the claimed method is not commensurate in scope with the claims is based on whether the claimed method enables a skilled artisan how to make and use, not how to test and screen. In this case, as previously made of record, the limitation of "Neublastin polypeptide" as recited in independent claim 80 also encompasses fragments, variants and derivatives of wild type Neublastin, SEQ ID

NO:12 based on the specification (see p. 2 of the instant specification). However, the specification provides insufficient guidance as to how to make and use these structurally undefined variants and derivatives.

In addition, the examiner asserts that the citation of Burgess is relevant because it teaches that any amino acid change in a growth factor would abolish the binding and activity of the growth factor, which is applicable to the instant Neublastin polypeptides that include variants and fragments of SEQ ID NO:12. The instant specification fails to provide sufficient guidance as to what other structures/amino acid sequences can or cannot be included/changed in all Neublastin polypeptides including fragments, variants and derivatives in order to preserve the activity of SEQ ID NO:12 and thus to be used in treating macular degeneration, retinitis pigmentosa or glaucoma. Thus, it is unpredictable whether all of the claimed Neublastin polypeptides including variants, derivatives and fragments can maintain their activity as that of SEQ ID NO:12.

Furthermore, claims 87-90 recite "an amino acid sequence of SEQ ID NOs:9-12", which encompasses different fragments with different sizes of amino acid sequences derived from the amino acid sequence of SEQ ID NOs:9-12. For the same reasons as set forth above, the specification also fails to provide sufficient guidance as to how to make and use these claimed sequences to preserve the neurotrophic activity as SEQ ID NO:12 because no teachings of specific conserved sequences and structures are provided.

Accordingly, a skilled artisan would not know how to make and use all of the Neublastin polypeptides including fragments, variants and derivatives in the claimed

method, indicating that undue experimentation is required to practice the claimed invention. Note that the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity is unpredictable and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03.

Claim Rejections - 35 USC § 112

10. Claims 80-83 and 87-93 stand also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons made of record.

On p. 14-15 of the response, Applicant argues that the claimed subject matter meets the written description requirement. Applicant argues that the claimed NBN polypeptides are structurally and functionally similar to SEQ ID NO:12 and the

specification provides descriptive essays, examples 1-3 and conserved amino acids and motifs. Applicant further cites Example 10 of the Written Description Guidelines Reversion1 in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the claimed NBN polypeptides used in the claimed method are not limited to the amino acid sequence of SEQ ID NO:12 or the amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:12 because the claimed polypeptides used in the claimed method encompass structurally undefined fragments, derivatives and variants derived from the amino acid sequence of SEQ ID NO:12. The specification only teaches Neublastin polypeptides comprising the amino acid sequences selected from SEQ ID NOs 9-12 that can be used in the claimed method. The specification fails to teach what other sequences or defined structures are required for the claimed polypeptides including fragments, derivatives and variants in order to preserve the neurotrophic activity of SEQ ID NO:12; and thereby to be used in the claimed method. Thus, the specification fails to reasonably demonstrate Applicant's possession of such broad genus of NBN polypeptides and thus Applicant is not in possession of the claimed method of using a broad genus of NBN polypeptide. Accordingly, the rejection of the claimed method for failing to meet the written description requirement is maintained.

Conclusion

11. NO CLAIM IS ALLOWED.

12. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
November 27, 2008

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649